Effect of Increased Radiotoxicity on Survival of Patients with Non-small Cell Lung Cancer Treated with Curatively Intended Radiotherapy

GEORG HOLGERSSON[1,2], STEFAN BERGSTRÖM[1,2], PER LIV1, JONAS NILSSON[1,2], PER EDLUND[2], CARL BLOMBERG[1,2], JAN NYMAN[3], SIGNE FRIESLAND[4], SIMON EKMAN[5], THOMAS ASKLUND[6], ROGER HENRIKSSON[6] and MICHAEL BERGQVIST[1,2,6]

[1]*Center for Research and Development, Uppsala University, Gävle Hospital, Gävle, Sweden;*
[2]*Department of Oncology, Gävle Hospital, Gävle, Sweden;*
[3]*Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden;*
[4]*Department of Oncology, Karolinska University Hospital, Stockholm, Sweden;*
[5]*Department of Oncology, Uppsala University Hospital, Uppsala, Sweden;*
[6]*Department of Radiation Sciences and Oncology, Umeå University Hospital, Umeå, Sweden*

Abstract. *Aim: To elucidate the impact of different forms of radiation toxicities (esophagitis, radiation pneumonitis, mucositis and hoarseness), on the survival of patients treated with curatively intended radiotherapy for non-small cell lung cancer (NSCLC). Patients and Methods: Data were individually collected retrospectively for all patients diagnosed with NSCLC subjected to curatively intended radiotherapy (≥50 Gy) in Sweden during the time period 1990 to 2000. Results: Esophagitis was the only radiation-induced toxicity with an impact on survival (hazard ratio=0.83, p=0.016). However, in a multivariate model, with clinical- and treatment-related factors taken into consideration, the impact of esophagitis on survival was no longer statistically significant (hazard ratio=0.88, p=0.17). Conclusion: The effect on survival seen in univariate analysis may be related to higher radiation dose and to the higher prevalence of chemotherapy in this group. The results do not suggest that the toxicities examined have any detrimental effect on overall survival.*

The number of patients with non-small cell lung cancer (NSCLC) in Sweden have increased during the last decades and today approximately 3,000 patients are diagnosed each year (1). Furthermore, the panorama of patients has shifted and the majority of patients are histologically-diagnosed with adenocarcinoma instead of squamous cell carcinoma, which was the dominating histology 20 years ago (2). Moreover, treatment for NSCLC has drastically changed during this time period and today, the intention in earlier stages of disease is curative rather than palliative, as previously. Amongst the different treatment options available, curatively intended radiation treatment in combination with chemotherapy is standard-of-care for the majority of patients with stage IIIA and in selected cases with stage IIIB disease (3). However, evaluation of these treatments in terms of toxicity and their implications on survival is limited. The aim of the study was to retrospectively investigate a large national cohort of patients with NSCLC who underwent curatively intended radiotherapy, in order to elucidate the impact of different forms of radiation toxicity on the outcome of the patients.

Correspondence to: Georg Holgersson, Ph.D. Student, MD, Department of Oncology, Gävle Hospital, SE-801 87 Gävle, Sweden. Tel +46 26154000, Fax +46 26154402, e-mail: Georg.Holgersson@regiongavleborg.se

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Patients and Methods

Patients. The present study was performed in collaboration between all the Swedish Oncology Departments. Data were collected for all patients diagnosed with NSCLC who were subjected to curatively intended radiotherapy (≥50 Gy) during the time period 1990 to 2000, based on a review of all the radiation charts at each individual Oncology Department. The study was reviewed and approved by a research ethical committee (Uppsala Research Ethics Committee, Dnr 2005: 025). The included patients were identified based on a manual search of all radiation charts and their medical records retrieved. This manual search was carried out by a reference group composed of five oncologists, who visited all the Oncology Departments and reviewed the charts together with the doctor responsible for the treatment of lung cancer at the specific site. Clinical data from all the Swedish Oncology Departments were

Table I. *Patient characteristics, treatment and adverse effects*.

	All patients	Hoarseness	Esophagitis	Mucositis	Radiation pneumonitis
All patients	682 (100%)	22 (3.2%)	266 (39.0%)	57 (8.4%)	91 (13.3%)
Gender					
Male	455 (66.7%)	13 (2.9%)	174 (38.2%)	34 (7.5%)	64 (14.1%)
Female	227 (33.3%)	9 (4%)	92 (40.5%)	23 (10.1%)	27 (11.9%)
p-Value		0.49	0.62	0.24	0.47
Age					
<55 years	121 (17.7%)	4 (3.3%)	50 (41.3%)	12 (9.9%)	16 (13.2%)
55-64 years	202 (29.6%)	8 (4%)	79 (39.1%)	17 (8.4%)	30 (14.9%)
65-74 years	258 (37.8%)	9 (3.5%)	102 (39.5%)	20 (7.8%)	34 (13.2%)
≥75 years	101 (14.8%)	1 (1%)	35 (34.7%)	8 (7.9%)	11 (10.9%)
p-Value		0.57	0.78	0.9	0.84
Histopathology					
Squamous cell carcinoma	357 (54.6%)	10 (2.8%)	131 (36.7%)	28 (7.8%)	47 (13.2%)
Adenocarcinoma	178 (27.2%)	9 (5.1%)	65 (36.5%)	14 (7.9%)	28 (15.7%)
Other	119 (18.2%)	2 (1.7%)	54 (45.4%)	13 (10.9%)	14 (11.8%)
p-Value		0.24	0.22	0.55	0.6
Missing	28	1	16	2	2
Time period					
1990-1995	299 (43.8%)	7 (2.3%)	99 (33.1%)	18 (6%)	43 (14.4%)
1996-2000	383 (56.2%)	15 (3.9%)	167 (43.6%)	39 (10.2%)	48 (12.5%)
p-Value		0.28	0.01	0.05	0.5
Stage					
IA	13 (2.2%)	0 (0%)	4 (30.8%)	1 (7.7%)	1 (7.7%)
IB	44 (7.5%)	1 (2.3%)	14 (31.8%)	5 (11.4%)	5 (11.4%)
IIA	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IIB	75 (12.9%)	1 (1.3%)	22 (29.3%)	13 (17.3%)	2 (2.7%)
IIIA	119 (20.4%)	3 (2.5%)	49 (41.2%)	7 (5.9%)	20 (16.8%)
IIIB	296 (50.8%)	12 (4.1%)	133 (44.9%)	23 (7.8%)	44 (14.9%)
IV	35 (6%)	2 (5.7%)	12 (34.3%)	4 (11.4%)	2 (5.7%)
p-Value		0.79	0.14	0.16	0.03
Missing	13 (2.2%)	0 (0%)	4 (30.8%)	1 (7.7%)	1 (7.7%)
Relapse (distant or local)					
Yes	448 (80.4%)	16 (3.6%)	188 (42%)	45 (10%)	48 (10.7%)
No	109 (19.6%)	2 (1.8%)	41 (37.6%)	6 (5.5%)	26 (23.9%)
p-Value		0.55	0.45	0.19	< 0.001
Missing	448 (80.4%)	16 (3.6%)	188 (42%)	45 (10%)	48 (10.7%)
Cause of death					
Lung cancer	479 (93.9%)	18 (3.8%)	189 (39.5%)	46 (9.6%)	59 (12.3%)
Other	31 (6.1%)	2 (6.5%)	10 (32.3%)	2 (6.5%)	9 (29%)
p-Value		0.35	0.46	0.76	0.01
Missing	172	2	67	9	23
Total dose					
<60 Gy	253 (37.6%)	6 (2.4%)	79 (31.2%)	14 (5.5%)	19 (7.5%)
≥60 Gy	420 (62.4%)	16 (3.8%)	187 (44.5%)	43 (10.2%)	72 (17.1%)
p-Value		0.38	< 0.001	0.04	< 0.001
Missing	9	0	0	0	0
Fraction size					
<2 Gy	208 (31%)	10 (4.8%)	108 (51.9%)	13 (6.2%)	29 (13.9%)
≥2 Gy	462 (69%)	12 (2.6%)	157 (34%)	44 (9.5%)	61 (13.2%)
p-Value		0.16	< 0.001	0.18	0.81
Missing	208 (31%)	10 (4.8%)	108 (51.9%)	13 (6.2%)	29 (13.9%)
Hyperfraction					
Yes	107 (18.4%)	2 (1.9%)	65 (60.7%)	12 (11.2%)	8 (7.5%)
No	474 (81.6%)	19 (4%)	162 (34.2%)	39 (8.2%)	68 (14.3%)
p-Value		0.40	< 0.001	0.34	0.06
Missing	101	1	39	6	15

Table I. *Continued*

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	All patients	Hoarseness	Esophagitis	Mucositis	Radiation pneumonitis
Induction chemotherapy					
Yes	128 (18.8%)	2 (1.6%)	67 (52.3%)	8 (6.2%)	18 (14.1%)
No	554 (81.2%)	20 (3.6%)	199 (35.9%)	49 (8.8%)	73 (13.2%)
p-Value		0.40	<0.001	0.38	0.77
Concomitant chemotherapy					
Yes	112 (17.0 %)	4 (3.6%)	67 (59.8%)	11 (9.8%)	17 (15.2%)
No	548 (83.0 %)	18 (3.3%)	198 (36.1%)	46 (8.4%)	73 (13.3%)
p-Value		0.78	<0.01	0.58	0.65
Any first line chemotherapy					
Yes	193 (29.0%)	6 (3.1%)	105 (54.4%)	14 (7.3%)	31 (16.1%)
No	473 (71.0%)	16 (3.4%)	160 (33.8%)	43 (9.1%)	59 (12.5%)
p-Value		1.00	<0.001	0.54	0.26

collected for 1344 patients in total. Patients who did not have a histopathological diagnosis date (n=173) and death date/last follow-up date (n=11), as well as patients treated with surgery (n=478), were excluded from analysis. Information regarding adverse effects of radiotherapy was available for the remaining 682 patients, and these were included in the analyses. The following variables were investigated: age, gender, time period for treatment, histopathology (defined as squamous cell carcinoma, adenocarcinoma or other non-small cell histopathology), stage (re-evaluated by three of the authors based on available information in the charts as well as based on available x-ray investigations), all given treatment (first line as well as subsequent treatment), radiotherapy regimen (dose, fractionation), adverse effects of radiotherapy (hoarseness, esophagitis, mucositis and radiation pneumonitis), occurrence of relapse and cause of death. Each adverse effect was defined as present or not present by the clinical judgment of the oncologists who reviewed the medical charts of the patients. Esophagitis was considered in patients with heartburn and dysphagia but it did not have to be endoscopically verified. Radiation pneumonitis was considered in patients with dyspnea and fever without any signs of infection and it was in most, but not all, cases radiologically verified. Mucositis was considered in patients with clinical signs of inflammation or ulceration in the oral mucosa. There was no grading of the adverse effects. In some patients, some of the data were missing which unfortunately causes inconsistencies among some of the frequencies accounted for in the results section of this article.

Statistics. Patients' characteristics at diagnosis are presented using standard descriptive statistics.

Overall survival was analyzed using Kaplan–Meier product-limit estimates. Log-rank tests were used to compare survival curves for patients with and without the examined adverse effects of radiotherapy. The follow-up time was calculated from the date of diagnosis to death or last follow-up until the end of 2008. Age was defined as age at diagnosis.

The association between overall survival and the adverse effects was also analyzed using univariate Cox proportional hazards regression models. A multivariate analysis was also performed with all adverse effects included in the model. The multivariate model was adjusted by gender, age at diagnosis, histopathology, stage, total radiation dose and fraction size and the addition of chemotherapy. Results are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). In addition, *p*-values are given, where $p<0.05$ was regarded as statistically significant. Assumption of proportional hazard was investigated by plotting scaled Schoenfeld residuals against time.

Results

Patients' characteristics and adverse effects. Out of the 682 patients included, 227 (33%) were women and 455 (66%) were men. The median age (range) was 66 (26-87) years. The most common histopathology was squamous cell carcinoma (n=357, 55%), followed by adenocarcinoma (n=178, 27%), whereas the rest of the tumors were classified as other NSCLC (n=119, 18%). The predominant clinical stage was stage IIIB, which made-up about half of the patient population (n=296, 51%). Among the adverse effects of treatment investigated (hoarseness, esophagitis, mucositis, radiation pneumonitis), esophagitis was the most prevalent, described in 266 (39%) of patients. Radiation pneumonitis was described in 91 (13%) of the patients whereas mucositis and hoarseness occurred in only 57 (8.4%) and 22 (3.2%) patients, respectively. The proportion of patients with radiation pneumonitis, esophagitis and mucositis were significantly higher in patients receiving ≥60 Gy ($p<0.05$). The proportion of patients with esophagitis was also significantly higher in patients receiving fraction sizes of <2 Gy and in patients treated during the years 1996-2000 as compared with those treated in 1990-1995 ($p=0.01$). The prevalence of esophagitis was significantly higher in patients receiving chemotherapy ($p<0.001$), both in the induction ($p<0.001$) and the concomitant setting ($p<0.01$). Chemotherapy (induction or concomitant) was given to 137 (37%) patients during the years 1996-2000 compared to 56 (19%) patients treated in 1990-1995. The proportion of patients with radiation pneumonitis was significantly lower in

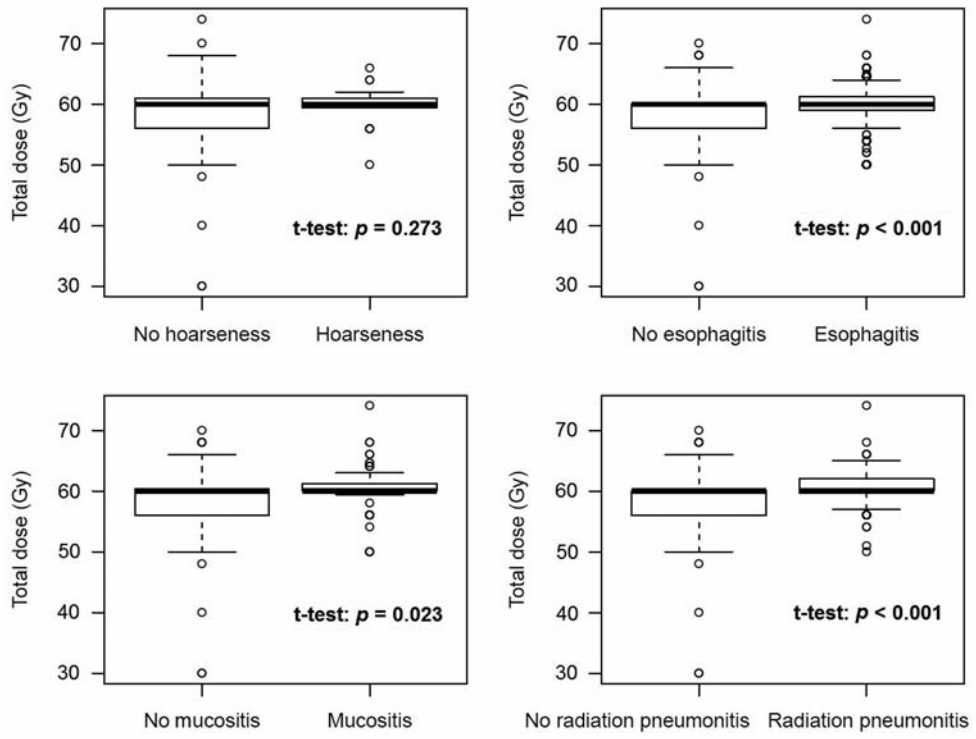

Figure 1. *Boxplots of total radiation dose (Gy) for patients with and without adverse effects. The boxes cover the interquartile range (IQR) and the thick band inside the box represents the median dose. The lower and upper whisker represent the largest and smallest values that are still within 1.5 times the IQR from its nearest quartile. Any observations that are more than 1.5 times the IQR away from the boxes are marked as circles.*

patients with disease relapse, whereas significantly higher in patients dying for reasons other than lung cancer ($p<0.001$ and $p=0.01$, respectively). For a summary of the clinical characteristics of the patients and the prevalence of adverse effects in different sub-groups of patients see Table I.

All adverse effects except hoarseness increased significantly with increasing total radiation dose and the largest effect was seen on the prevalence of radiation pneumonitis and esophagitis ($p<0.001$). The relationship between total radiation dose and prevalence of the adverse effect is shown in boxplots in Figure 1.

Survival and adverse effects. The median overall survival for all patients was 11.4 months. When comparing survival of patients with against those without adverse effects of radiotherapy, patients with esophagitis had a statistically significantly ($p=0.016$, log-rank test) better overall survival compared to patients without esophagitis (median survival 13.3 months *vs*. 11.2 months). For the other adverse effects, no statistically significant impact on overall survival was seen (see Figure 2). For details regarding overall survival and the impact of adverse effects, see Table II. The impact of esophagitis on survival was also seen in a univariate Cox regression analysis of overall survival (HR=0.83, $p=0.016$). However, in a multivariate model which was adjusted by gender, age at diagnosis, histopathology, stage, total radiation dose, fraction size and the addition of chemotherapy, the impact of esophagitis on survival was no longer statistically significant (HR=0.88, $p=0.17$). The univariate and multivariate Cox models are shown in Table III and IV, respectively.

Discussion

In the present study, we investigated the toxicity profiles of patients treated with curatively intended radiotherapy for NSCLC during 1990-2000. We showed that an increased total radiation dose, as expected, is associated with a higher proportion of patients with adverse effects, in particular, esophagitis and pneumonitis. We further showed that the prevalence of adverse effects examined does not imply a worse prognosis in terms of overall survival. For patients with esophagitis, there was instead a significant correlation with longer overall survival that was, however, not retained in a multivariate analysis where other patient- and treatment-related factors were taken into consideration.

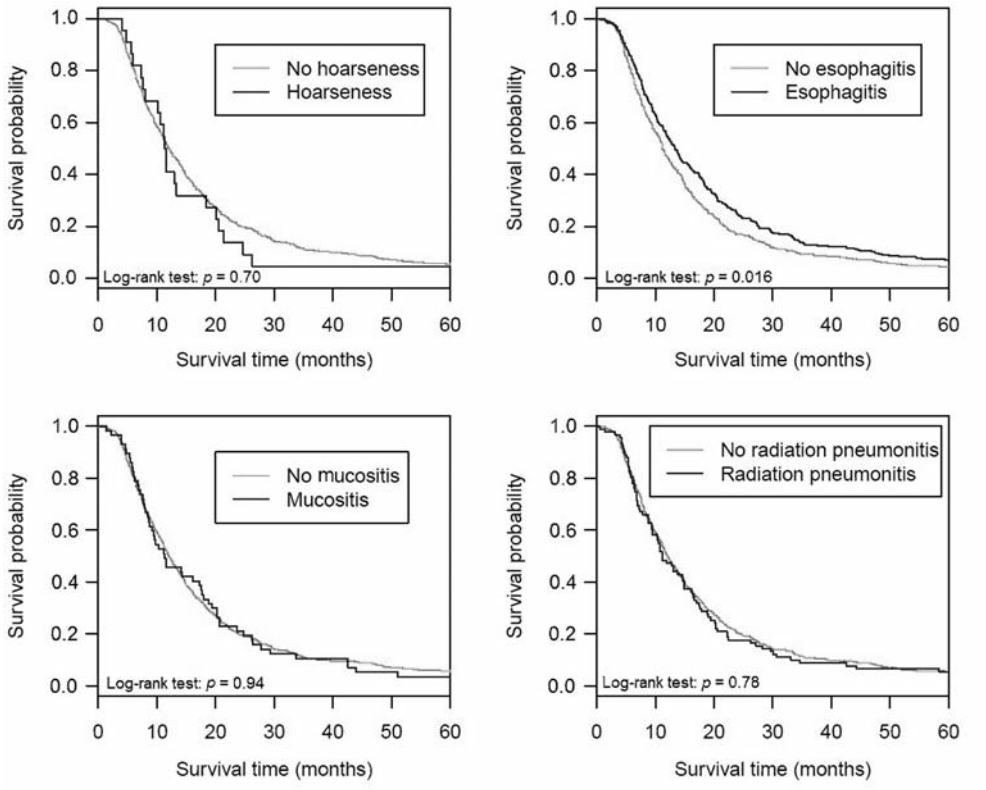

Figure 2. *Kaplan-Meier plots of overall survival for patients with and without adverse effects.*

Table II. *Estimated median survival and 5-year survival rate for different sub-groups.*

Strata	N	Median survival in month (95% CI)	5-year survival rate (95%CI)
All patients	682	11.4 (10.2, 20.0)	5.45% (3.97, 7.46)
Hoarseness	22	11.4 (10.2, 20.0)	4.55% (0.67, 30.85)
No hoarseness	660	12.0 (11.2, 13.3)	5.47% (3.98, 7.53)
Esophagitis	266	13.3 (11.8, 15.6)	7.01% (4.51, 10.89)
No esophagitis	416	11.2 (10.6, 12.5)	4.45% (2.84, 6.97)
Mucositis	57	11.3 (8.67, 17.7)	3.50% (0.90, 13.69)
No Mucositis	625	12.0 (11.20, 13.1)	5.63% (4.07, 7.78)
Radiation pneumonitis	91	11.2 (9.46, 14.9)	5.49% (2.34, 12.88)
No radiation pneumonitis	591	12.0 11.24, 13.3)	5.44% (3.87, 7.63)

The present study including 682 patients is unique both in terms of size of the cohort and its population-based character, as well as in the review of individual charts with a long follow-up period. All patients diagnosed with NSCLC and given curatively intended radiotherapy during 1990-2000 in a well-defined geographical area with a common healthcare system (Sweden) were included. A reference group composed of five oncologists visited all sites and in collaboration with the medically responsible doctor at the specific site reviewed all charts.

However, it should be emphasized the present study has some limitations. One of the most obvious is the data retrospectively collected directly from the clinical charts. Moreover, only patients with data regarding radiation toxicity were included, which may lead to selection bias. Furthermore, since the toxicity data are only of qualitative nature, we cannot evaluate the impact of the grade of toxicity on survival outcome. We are also lacking dose–volume data for organs at-risk for toxicity.

It could be speculated from the present results whether increased toxicity may be a surrogate marker for increased

Table III. *Univariate Cox regression analysis of overall survival*

Variable	Number of patients	Hazard ratio (95% CI)	*p*-Value
Hoarseness	22	1.09 (0.71-1.67)	0.700
Esophagitis	266	0.83 (0.71-0.96)	0.016
Mucositis	57	1.01 (0.77-1.33)	0.943
Radiation pneumonitis	591	1.03 (0.82-1.29)	0.782

Table IV. *Multivariate Cox regression analysis of overall survival.*

Variable	Hazard ratio (95% CI)	*p*-Value
Gender		-
Female	Reference	
Male	0.93 (0.76-1.13)	0.47
Age		
Age <50 years	Reference	
Age 55-64 years	1.21 (0.92-1.60)	0.18
Age 65-74 years	1.38 (1.04-1.82)	0.023
Age ≥75 years	1.08 (0.77-1.51)	0.66
Histopathology		
Adenocarcinoma	Reference	
Squamous cell carcinoma	1.20 (0.97-1.48)	0.096
Other	1.25 (0.96-1.64)	0.098
Stage	1.11 (1.04-1.20)	0.0016
Fraction size		
<2 Gy	Reference	
≥2 Gy	1.11 (0.91-1.35)	0.29
Total radiation dose		
<60 Gy	Reference	
≥60 Gy	0.84 (0.69-1.01)	0.067
Any first line chemotherapy		
No	Reference	
Yes	0.83 (0.67-1.04)	0.11
Esophagitis	0.88 (0.73-1.06)	0.17

effect of radiation treatment. There exist, to the knowledge of the authors, no previous studies that have dealt with the direct impact of radiation-associated toxicities on overall survival in patients with NSCLC treated with curatively intended radiotherapy. A prospective study by Dehing-Oberije *et al.* showed that age, gender, concurrent chemotherapy, overall treatment time, mean esophageal dose and maximum esophageal dose correlated to the development of dysphagia when treating lung cancer (4). In general, it is accepted that an increased radiation dose is associated with increased survival (5-8). However, the RTOG 0617 study recently showed a detrimental effect of higher radiation dose (9), thus demonstrating the complexity in comparing various studies.

In the present study, the dominating radiation-induced toxicity was esophagitis, which is a common adverse effect in patients with lung cancer treated with concurrent chemoradiation therapy. In line with our results, Palma *et al.* (10) showed that patients with non-small cell lung cancer treated with concurrent chemoradiation therapy were affected by esophagitis in a dose-dependent manner, with an increased risk of high-grade esophagitis when receiving ≥60 Gy to the esophagus. This was also seen in the study by Belderbos *et al.* (11), in which esophageal volumes receiving at least 35 Gy had an increased risk of developing acute esophageal toxicity. It was also shown that concurrent chemoradiation therapy increased the acute esophageal toxicity compared to radiotherapy alone. Regarding fraction size, our results showed that esophagitis was significantly more prevalent in patients receiving <2 Gy per fraction and in patients receiving hyperfractionated radiotherapy. These findings are in accordance with the results from the ECOG 2597 study, comparing conventionally fractionated radiotherapy with hyperfractionated radiotherapy, in which a higher rate of grade 3-4 esophageal toxicity was found in the hyperfractionated radiotherapy-treated group (12).

Esophagitis was significantly more prevalent in patients receiving chemotherapy as induction or as concomitant treatment. The addition of chemotherapy was in turn independently associated with increased overall survival in the multivariate Cox analysis, whereas esophagitis was not. In addition, both esophagitis and the addition of chemotherapy was significantly more prevalent during the years 1996-2000 compared to patients treated between 1990-1995. Thus, it seems that the increased survival in patients with esophagitis seen in the univariate analysis to some extent can be explained by an effect of a higher degree of chemoradiotherapy in these patients, which is well, established as being superior to radiotherapy alone (13).

Our results also show that the encountered radiation pneumonitis was significantly negative correlated to disease relapse, and positively correlated to patients dying for other reasons than lung cancer, but not significantly correlated to overall survival. The proportion of patients with radiation pneumonitis was significantly higher when receiving ≥60 Gy. A recent study by Dang *et al.* (14), who analyzed risk and predictors for early radiation pneumonitis in 369 patients with stage III NSCLC, found a significant correlation between radiation pneumonitis and response to treatment. Our results in line with this, and may further indicate that higher doses of radiation therapy can be predictors of response to treatment and that radiation pneumonitis may also be a surrogate marker for therapy response.

Furthermore, esophagitis was significantly associated with longer duration of overall survival, but this result was not retained in the multivariate model adjusted by gender, age at diagnosis, histopathology, stage, total radiation dose, fraction size and the addition of chemotherapy. Thus, the effect on

survival might just be a question of higher dose or the effect of the addition of chemotherapy. Importantly in the clinical setting, these results do not suggest that the toxicities examined have any detrimental effect on overall survival. The encountered esophagitis may simply indicate that a higher radiation dose was delivered. Thus, an increased total radiation dose with associated increased toxicity was not obviously associated with overall survival.

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